



Bariatric surgery and hypertension: implications and perspectives after the GATEWAY randomized trial

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What is the problem in obese patients with hypertension?

Obesity prevalence has presented an exponential increase in the last years, becoming a serious public health issue (1). Moreover, patients with an increased body mass index exhibit different comorbidities, including hypertension, which are tightly related to the high cardiovascular risk of this population (2). In the United States, half of the patients with hypertension display obesity. Moreover, a third of obese subjects have high blood pressure levels, compared to the 20% observed in subjects with a normal body mass index (3). Furthermore, the intervention strategy for hypertension in patients with obesity implies various challenges concerning the effect of the pharmacological treatment. In this respect, obesity leads to a resistance to antihypertensive medication together with disturbances in volume distribution and hepatic and renal clearance (4). This implies that patients with hypertension and obesity in general require a more “aggressive” antihypertensive treatment in order to achieve desirable blood pressure levels.

What was known about the effects of weight loss therapies on hypertension?

The low efficacy of lifestyle modifications and exercise as a treatment for obesity has been widely described (5).

This can be explained, at least in part, due to the difficulty in adhering to lifestyle changes in these patients. On the other hand, bariatric surgery has proved to be the most effective therapy for patients with severe obesity, achieving a greater weight loss than that obtained with conventional treatment (6) and favouring the remission of obesity-related comorbidities (7). In this respect, Roux-en-Y gastric bypass has been considered the gold standard technique due to the favourable results obtained both on weight loss and comorbidity remission, including hypertension. The effect of bariatric surgery on hypertension remission has been analyzed in various observational studies, some metanalysis and scarce randomized controlled trials (8-12). The findings of these studies consistently showed an improvement in hypertension one year after bariatric surgery, with remission rates above 60–70%. As to a longer-term follow-up, the recent cohort study published by Jakobsen *et al.* (13) compared bariatric surgery (92% gastric bypass) versus medical treatment with a median follow-up of 6.5 years. Hypertension remission was 31.9% in the surgical group in comparison to 12.4% in the medical group.

Moreover, apart from weight loss, several weight-independent factors have also been described that could play a role in comorbidity remission, as has been studied for type 2 diabetes. In the case of hypertension, a decreased inflammatory response together with an improvement in insulin resistance could decrease arterial stiffness and

sodium reabsorption, and hence lead to normalization in blood pressure levels (14). In addition, an increase in gastrointestinal gut hormones such as peptide YY and glucagon-like peptide-1 could also be involved in hypertension remission, due to their effects both on the gastrointestinal system together with a diuretic and natriuretic effect on the kidney (15).

However, it must be highlighted that previous randomized controlled trials comparing comorbidity remission between bariatric surgery and conventional therapy had focused mainly on type 2 diabetes, although some had also included hypertension as a secondary endpoint.

What is new in the GATEWAY study?

In the GATEWAY (Gastric Bypass to Treat Obese Patients With Steady Hypertension) randomized trial reported by Schiavon *et al.* in *Circulation* in March 2018 the effects of gastric bypass on hypertensive patients with obesity were analyzed (16). Patients with hypertension (using ≥ 2 medications at maximum doses or >2 at moderate doses) and a body mass index between 30.0 and 39.9 kg/m² were randomized to Roux-en-Y gastric bypass plus medical therapy or medical therapy alone. The primary endpoint ($\geq 30\%$ reduction of the total number of antihypertensive medications while maintaining systolic and diastolic blood pressure <140 and 90 mmHg, respectively, at 12 months) occurred more frequently in the gastric bypass group (83.7%) in comparison to the control group (12.8%). Moreover, hypertension remission, defined as systolic and diastolic blood pressure <140 and 90 mmHg, respectively, with previous withdrawal of all medication, occurred in about half of the patients submitted to the gastric bypass group and none in the conventional treatment group.

The relevance of this study is mainly related to its design, as it is the first randomized controlled trial aimed at evaluating the effect of bariatric surgery on hypertension. Moreover, it only includes patients with hypertension that require an “aggressive” antihypertensive treatment. Hence, in the hypothetical case that bariatric surgery is primarily indicated to control refractory hypertension, the chance of achieving remission would be close to 50%. It is worth emphasizing that these remission rates are lower than those described in previous reports, as these included patients with “milder” hypertension that were controlled with one or none antihypertensive medication.

Moreover, this remission rate also seems to decrease

with a longer-term follow-up, as observed in the previously mentioned study by Jakobsen *et al.* (13). In this publication, hypertension remission was almost 32% in the surgical group, compared to the nearly 50% one-year post surgery in the present GATEWAY trial.

Some limitations of the present GATEWAY trial must also be highlighted. In the first place, patients included in the trial had a body mass index 30–39.9 kg/m², and thus don't strictly follow the indications for bariatric surgery of general guidelines. Moreover, the sample size was limited, as of the 1,489 patients assessed for eligibility, only 96 were included in the main analysis.

What will be next?

Despite the high relevance of the results of the GATEWAY trial, some issues concerning the effect of bariatric surgery on hypertension are still awaiting an answer. First, little is known about the mid (3–5 years) and long (>5 years) term effects of bariatric surgery on hypertension remission. In type 2 diabetes mellitus, randomized controlled trials have shown that some patients with remission at 1 year after bariatric surgery presented diabetes relapse at 5 years follow-up (17,18). Regarding hypertension, observational studies indicate that blood pressure also worsens after the first year following surgery, in parallel to weight regain. In accordance with these findings, a previous study from our group with a 36-month follow-up observed that 21.9% of the patients who had hypertension remission at 12 months after surgery presented a relapse at 3 years (12). Moreover, weight loss was one of the independent factors associated to hypertension relapse. Therefore, the results of the GATEWAY trial extension will be extremely useful to confirm or contrast these previous observations.

On the other hand, it would also be of great interest to identify preoperative predictors of hypertension remission after bariatric surgery. This information would help the physician prescribing bariatric surgery and the patient in order to settle real expectations before the procedure. In type 2 diabetes mellitus, the remission-associated factors have been widely described and are basically related to beta cell functionality and diabetes treatment (19). Hence, those patients with low C peptide levels before surgery or those receiving treatment with various antidiabetic drugs or insulin have a lower probability of achieving type 2 diabetes mellitus remission. Similarly, in the previously mentioned study of our group, the number of antihypertensive drugs prior to surgery was inversely related with hypertension

remission after the procedure (12).

Finally, it would also be necessary to evaluate the differential effect of the various bariatric surgery techniques on hypertension remission. In this respect, the use of laparoscopic sleeve gastrectomy has been increasing in the last ten years owing to its technical simplicity and similar short-term results to those of laparoscopic Roux-en-Y gastric bypass, in terms of weight loss and comorbidity remission. These advantages placed laparoscopic sleeve gastrectomy for the first time as the most widely used bariatric surgery technique worldwide in 2014 (20). Two randomized clinical trials comparing 5-year results of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy have been recently published (21,22). Contradictory results were obtained, as the SM-BOSS trial found no differences between both surgical procedures regarding hypertension remission (21), whereas the SLEEVEPASS trial showed greater remission rates after laparoscopic Roux-en-Y gastric bypass in comparison to laparoscopic sleeve gastrectomy (22). However, it is worth mentioning that in both trials' hypertension remission was, once again, a secondary end-point. Moreover, there were differences in baseline characteristics of patients included in the study groups and there were also discrepancies regarding the criteria used to define hypertension remission in the two trials. Therefore, future randomized trials comparing both surgical procedures with a primary end-point aimed at evaluating hypertension remission at short, mid and long-term are mandatory to shed more light on this matter.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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